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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,135	12/11/2003	Charles Joel Arntzen	P00245US17	8272

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EXAMINER	
WORLEY, CATHY KINGDON	
ART UNIT	PAPER NUMBER
1638	
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07/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,135	ARNTZEN ET AL.	
	Examiner	Art Unit	
	CATHY K. WORLEY	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed March 26, 2008, has been entered.

2. Claims 11-16 have been cancelled.

3. Claims 1-10 are pending and are examined in the present office action.

4. The text of those sections of Title 35, U.S. Code not included in this office action can be found in a prior office action.

Rejections that are Withdrawn

5. The rejection of claims 1-10 and 15 for nonstatutory obviousness-type double patenting over US Patent No. 5,792,935 is withdrawn in light of the terminal disclaimer received on Mar. 26, 2008.

Claim Rejections - 35 USC § 103

6. After further consideration and in light of the ruling in *KSR*, 82 USPQ2d at 1396, the rejection of claims 1-5 and 7-10 under 35 U.S.C. 103(a) as being unpatentable over Goodman et al (US Patent No. 4,956,282, issued on Sept. 11, 1990) in view of Kapikian et al (Reviews of Infectious Diseases (1989) Vol. 11, supplement 3, pp. S539-S546) is reinstated for the reasons of record stated in the previous Office Action mailed on Jan. 18, 2007, and the reasons stated below. The

Applicant's arguments in the response filed on June 20, 2007 were fully considered but were not found to be persuasive.

The claims are drawn to a method of producing an immunogenic composition, wherein said method comprises the steps of transforming a plant with a nucleic acid encoding a recombinant viral immunogen, and producing from said plants said composition. Claim 1 includes "selecting those plants expressing said recombinant viral immunogen at a level such that upon oral administration of a composition comprising a plant-expressed recombinant viral immunogen to an animal, an immunogenic response to said viral immunogen is elicited". The office interprets this recitation to be inclusive of any expression level because the composition can comprise recombinant viral immunogen that has been purified and/or concentrated; therefore the amount of immunogen in the composition is not related to the level of expression in the plant. Therefore, this part of the claim is not considered a further limitation. Claim 4 contains similar language and is therefore inclusive of plants with any expression level.

Goodman et al teach the production of recombinant proteins in plants, including proteins encoded by mammalian viral pathogen genes (see column 3, lines 11-13). They suggest that antigens associated with viral pathogens could be expressed (see column 3, lines 31-32). Antigens are also referred to in the art as immunogens (see page 9 of the instant specification, line 2). They teach that in some instances the recombinant protein can have a physiological effect on ingestion,

and it will be sufficient for the product to be retained in an edible plant part (see column 5, lines 51-56). They teach that plants that can be employed for the production of recombinant proteins may be either monocots or dicots (see column 4, lines 55-56), that the DNA construct can be transferred into the plant cell by *A. tumefaciens*, or *A. rhizogenes*, microinjection, liposome fusion, or viral infection (see column 4, lines 43-45) which are all means of transforming a plant with a construct. Goodman et al teach transcriptional initiation regions (also referred to as promoters), including the napin promoter for expression in seeds (which is an edible tissue of a plant) (see column 2, lines 43-58). They suggest the use of several different species of plants that are edible by an animal, including sunflower, corn, sugar cane, soybean, tomato, alfalfa, mustard, and sugar beet (see column 4, lines 59-60).

Goodman et al do not teach an immunogen from a transmissible gastroenteritis virus, nor do they teach an immunogen that is capable of generating an immunogenic response when it interacts with a mucosal membrane.

Kapikian et al teach an immunogen from a transmissible gastroenteritis virus that is capable of generating an immunogenic response when it interacts with a mucosal membrane, (see pages S542-S543 for a discussion of candidate vaccines, and see page S542, right column, last paragraph, where is states that the vaccine was shown to be safe and antigenic after oral administration which shows that is

generates an immunogenic response when it interacts with a mucosal membrane). This demonstrates that it has a physiological effect on ingestion.

Given the recognition of those of ordinary skill in the art of the value of expressing an immunogenic protein in a plant as taught by Goodman et al (see column 3, lines 31-32), it would have been obvious to one of ordinary skill in the art to use the method of Goodman et al and to modify said method using the sequences encoding the immunogens taught by Kapikian et al. One would have been motivated to express the immunogens taught by Kapikian et al because they teach that it is important to find a safe, inexpensive, and effective rotavirus vaccine (see page S539, left column, first paragraph) because such a vaccine can prevent diarrheal diseases that cause about 12,600 deaths per day (see page S539, paragraph bridging left and right columns). Furthermore Kipikian et al specifically state that an orally administered vaccine would be the most effective (see page S541, left column, first paragraph) and Goodman et al specifically suggest that their method can be utilized to grow recombinant viral antigens (see column 3, lines 31-35) and they teach that it could be used for expression in an edible plant part for proteins that can have a physiological effect on ingestion (see column 5, lines 51-56). In addition, it would have been obvious to select the plants with the highest expression levels; and the highest producers would have the ability to generate an immunogenic response sufficient to protect against a viral challenge after oral administration of the plant or plant parts. Given the success of producing

recombinant therapeutic proteins in plants taught by Goodman et al and the success of utilizing recombinant proteins for vaccines as taught by Kapikian et al, one would expect success in combining the teachings.

Thus, the claimed invention would have been *prime facie* obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

APPLICANT'S ARGUMENTS

The Applicant argues that the prior art does not teach the step of selecting the plants expressing the recombinant viral immunogen at a level such that upon oral administration an immunogenic response to the immunogen is elicited (see page 19 of the response filed on June 20, 2007). This is not persuasive, however, because it is obvious to select for the plant with the highest production, and the highest production of recombinant protein would have the ability to elicit an immune response.

The Applicant argues that the board of patent appeals and interferences (BPAI) ruled that Goodman did not teach expression of an immunogenic protein in a plant in their decision in Ex parte Roy Curtiss III and Guy A. Cardineau, Appeal No. 93-4341, heard on Jan. 11, 1996 (see pages 19-20 of the response). This is not persuasive, however, because this ruling was not a precedential ruling and the fact pattern in the previous case is not identical to the fact pattern in the instant application nor is the previous rejection identical to the present rejection.

The Applicant argues that Kapikian fails to supply the teachings that are lacking in Goodman (see third paragraph on page 20 of the response), presumably this deficiency is the lack of teaching that an immune response is elicited upon ingestion. This is not persuasive, however, because Kapikian et al specifically teach that oral administration of their vaccine against gastroenteral viruses is the preferred delivery; and Goodman et al specifically teach that if the recombinant protein has a physiological effect upon ingestion, then it does not need to be purified out of the edible plant parts. Therefore, there is no deficiency in the combination of the two references.

The Applicant argues that Goodman teaches expression of a dental bacterial antigen not a viral mammalian protein and that Goodman contemplates the use of transgenic plants to produce non-immunogenic proteins that are not vaccines (see third paragraph on page 21 of the response). This is not persuasive, however, because the working example provided by Goodman et al is only one embodiment of what they have contemplated, and they clearly state that their method can be used to produce vaccines; including mammalian viral pathogens (see column 3).

The Applicant further argues that Kapikian does not teach plants expressing viral immunogenic proteins (see last paragraph on page 21 of the response). This is not persuasive, however, because the rejection is based on the combination of the two references rather than on Kapikian, individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by

attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

7. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goodman et al (US Patent No. 4,956,282, issued on Sept. 11, 1990) in view of Kapikian et al (Reviews of Infectious Diseases (1989) Vol. 11, supplement 3, pp. S539-S546), as applied to claims 1-5 and 7-10 above, and further in view of Kay et al (Science (1987), Vol. 236, pp. 1299-1302), and further in view of Gallie et al (MGG (1991), Vol. 228, pp. 258-264).

The claims are drawn to a method of producing an immunogenic composition, wherein said method comprises the steps of transforming a plant with a nucleic acid encoding a recombinant viral immunogen and comprising a 5' untranslated leader sequence and an enhancer; and producing from said plants said composition.

Goodman et al in view of Kapikian et al have been discussed above. In addition, Goodman et al specifically teach that expression can be directed to a particular plant part such as roots, leaves, stalk, or the like (see column 2, lines 35-37) and they specifically mention the napin promoter or other seed protein promoter for expression in seeds (see column 2, lines 54-58). Depending on the plant, roots, leaves, and seeds can be edible tissues.

Goodman et al in view of Kapikian et al do not teach the use of a 5' untranslated leader sequence, nor do they teach an enhancer sequence.

Kay et al teach the use of an enhancer from the CaMV 35S upstream sequences (see page 1299, middle column).

Gallie et al teach the use of a 5' untranslated leader sequence (see page 258, right column).

Given the recognition of those of ordinary skill in the art of the value of utilizing and enhancer as taught by Kay et al and a 5' untranslated leader sequence as taught by Gallie et al, it would have been obvious to one of ordinary skill in the art to use the method of Goodman et al and to modify said method by using the enhancer taught by Kay et al and the 5' untranslated leader sequence taught by Gallie et al and by expressing the immunogens taught by Kapikian et al.

One would have been motivated to utilize an enhancer because Kay et al teach that the presence of the enhancer leads to 40-fold higher levels of expression of a transgene (see page 1301, left column, first paragraph).

One would have been motivated to use a leader sequence because Gallie et al teach that a leader sequence substantially enhances translation of a gene construct (see page 258, right column, second paragraph).

One would have been motivated to express the immunogens taught by Kapikian et al because they teach that it is important to find a safe, inexpensive, and effective rotavirus vaccine (see page S539, left column, first paragraph) because

such a vaccine can prevent diarrheal diseases that cause about 12, 600 deaths per day (see page S539, paragraph bridging left and right columns). Given that Kapikian et al teach that these vaccines can be orally administered and Goodman et al teach that if the particular recombinant protein has a physiological effect upon ingestion then it will not be necessary to purify it out of the edible plant parts, one would have been motivated to express the vaccine in edible plant parts.

Given the successes taught in the prior art, one would expect to succeed in expressing a recombinant viral immunogen utilizing a nucleic acid construct comprising a leader sequence and an enhancer in the method taught by Goodman et al.

Thus, the claimed invention would have been *prime facie* obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

The Applicant argues that because claim 1 is not obvious, then dependent claim 6 can not be obvious (see pages 22-23 of the response). This is not persuasive, however, because claim 1 is obvious over the prior art (see discussion, above).

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cathy K. Worley whose telephone number is

(571) 272-8784. The examiner is on a variable schedule but can normally be reached on M-F 10:00 - 4:00 with additional variable hours before 10:00 and after 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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